GUEST PERSPECTIVES

Exploring the Genomics Frontier

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The year is 2015. The results of genetic screening tests have just been returned to your family physician. Because you need particular medications, the tests identified metabolic abnormalities that could affect your response to specific drugs, allowing your doctor to "individualize" your treatment. You also opted for a screen for genetic susceptibility to environmental toxins. Even in 2015, this test is not covered by insurance plans, making it available only to the fairly wealthy (though a trust fund has been set up by the environmental justice movement to subsidize testing for low-income people). Here is what you learn. You have a higher than average sensitivity to two fairly ubiquitous pollutants as well as a chemical you have been exposed to for the past twenty years in your workplace. You are given a list of products, foods, and cosmetics that you need to avoid in the future because of their chemical composition and sent on to an "environmental counselor" (trained and certified by EPA) to discuss particular strategies you can use to reduce exposure and risk.

This future world is one of convergence, between toxicology and pharmacology, between environmental science and medicine, and between social regulation and personal revelation and responsibility. This world will rise up from the cracks between disciplines, organizations, and comfortable belief systems, and will, frankly, startle us. The outlines of such a future world are visible today, though the exact timing, desirability, and paths to this future scenario can be many and varied.

Over the past twenty years, the world of environmental risk has become more precisely mapped, revealing sensitive sub-populations that require special care: the very young, those with immune deficiencies, nursing mothers, or racial and ethnic groups that suffer from environment "injustice." This risk map, however, will appear pre-Columbian when compared to emerging maps drawn with the genomics pen. The most aggressive cartographers of this new world live in the pharmaceutical industry, but over the next decades they will be joined by environmental scientists and others searching for a better understanding of the relationship between changes in genes and proteins and the potential for good or adverse effects.

Where should we focus our limited attention and resources? First of all, expect and prepare for surprises, especially *spill over* or *second order effects* from other areas. In this regard, pharmaceutical research needs to be carefully watched. Of great interest to drug developers is the identification of people who, because of differences in metabolism, may not respond to drugs or respond with adverse effects. Drug manufacturers are focusing significant amounts of research on the function of six cytochrome enzymes responsible for the metabolism of nearly all clinically useful medications (a list of drugs metabolized by these enzymes can be found at: http://medicine.iupui.edu/flockhart). Genetic abnormalities in the genes controlling these enzyzmes can also decrease an individual's ability to detoxify carcinogens and other chemicals in the environment, thus increasing health risks. It is highly likely that genomic techniques being developed for pharmaceuticals will shed light on how our bodies deal with toxic substances. This, in fact, is already happening and "collateral information" developed through pharmacogenomic research may provide the initial basis for identifying at risk sub-populations based on metabolic abnormalities.

In addition, we may find genetic deficiencies that result in highly specific toxic sensitivities. Scientists have identified a gene variation that raises the risk of lung disease from exposure to beryllium by nearly 30 times over that of the

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general population. High levels of beryllium exposure are confined largely to those working on the manufacture of nuclear weapons, but the discovery of a gene mutation increasing susceptibility to a specific toxic raises some interesting issues. For instance, how many more genes like this will be discovered and what if similar genetic susceptibilities are discovered for highly common and ubiquitous pollutants? Mutations in the genetic coding for the enzyme α_1-antitripsin, for example, can exacerbate the effects of particulates leading to the development of chronic obstructive pulmonary disease.

If genetically-based susceptibility differences vary by a factor of 20 or 30 for various pollutants, will existing exposure safety factors suffice to protect highly vulnerable sub-populations? Normally, EPA standards assume a 10-fold uncertainty factor for inter-individual variation to calculate the reference dose or concentration for non-carcinogens. This possibility raises serious questions concerning our society's capacity to protect newly identified populations of genetically sensitive people if the technologies to adequately reduce emissions and exposures do not exist, or would be prohibitively expensive to implement. The opposite scenario is also possible, that mounting genetic evidence could indicate that safety factors have been set too high for specific chemicals resulting in over-regulation and excessive costs to industry. In this situation, would a rollback of regulatory standards be politically possible?

Even if we could achieve a micro- or zero emissions society, people will continue to be exposed to toxins through their consumption and use of products and genetic sensitivities will remain an issue. Diet Coke already uses a warning label for phenylketonurics, individuals with a genetically-based sensitivity to artificial sweeteners affecting only one in 15,000 people. This is the tip of an emerging genetic labeling iceberg and one can only image the labels that may exist in 10-20 years as research progresses.

If we follow this slippery slope a bit further, we arrive at a future world where we are forced to increasingly move the responsibility for environmental protection away from society and onto the individual. Regulation must be increasing complemented by counseling and education, areas where the government has no legal foothold and far less experience.

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Predictions are difficult because trends will often be affected by discontinuities, but here are some possible features of the emerging genomic landscape.

- Genomic technologies will rapidly become cheaper and ubiquitous (not confined to research labs and academic settings).
- Surprises will come from unexpected directions, spilling over from clinical applications, drug development, and rapid advances in the technologies themselves.
- New stakeholders will appear in terms of those who supply the data, want the data, and control the technologies (doctors, pharmaceutical companies, insurers, HMOs, etc.)
- Technological advances will far outpace the underlying science.
- Data interpretation will remain difficult in the near future, however that will not prevent its use and misuse (in the courts, in the press, and by special interests).
- The largest challenges will not be in the area of science, but education, communication, and outreach.
- The ethical, legal, and social issues will be profound.
- The existing environmental workforce (especially the policymaking community) is unprepared.

So how does the government prepare for this future, or, for those who believe in the need for proactive governance, how does the government shape this future? The biologist Garrett Hardin once observed that in a system, you can never do just one thing. This adage holds true for the

social and institutional systems that create public policy. Shaping the emerging science and technologies will require proactive governance focused simultaneously on multiple areas. Here are a few of the important focal points.

- **Create more effective science/policy interfaces for toxicogenomics.**

It should be obvious from the previous explorations, that there is a wide range of players in this new world who need to talk, cooperate, plan, and implement programs on an on-going basis. These stakeholders have, at the moment, no regular mechanism to interact on key science and policy matters. The toxicogenomic science agenda will be driven largely by the National Institute of Environmental Health Sciences (NIEHS). The NIEHS has recently awarded five-year grants totaling more than $37 million to five research centers across the U.S. — by far the largest single amount focused on toxicogenomics.

However, in order for the science to have broad ranging social impacts, this new knowledge must be translated into new regulatory approaches and eventually into technological applications capable of being diffused widely in the marketplace, tasks that will depend much more on EPA in the environmental arena. The EPA and NIEHS should explore mechanisms to ensure closer cooperation, including interactions with FDA, OSHA, and other stakeholders, where appropriate (a greater use of the Intergovernmental Personnel Act should be explored to facilitate the continual exchange of people between federal entities). Within EPA, ongoing mechanisms (such as the Science Policy Council) must continually and aggressively bridge the extramural science and emerging technologies with challenges faced by the program offices dealing directly with toxics, air, water, and radiation issues.

- **Develop a program to harmonize and standardize data, testing procedures, and technologies.**

At the present time many sources of variation exist that would make the application of genomics data and technologies (such as DNA arrays) difficult in a regulatory setting. These include variation arising in the preparation of DNA samples for analysis and variance between different analytical arrays produced by different manufacturers and laboratories. Given these variations, it will be difficult to sort artifact out from real adverse change in organisms or ensure reproducibility of results and ultimately, applicability of the data to regulatory decision-making. A large number of stakeholders will need to be comfortable with the accuracy, reproducibility, and predictive capacity of these genomic methods, including EPA, other agencies such as OSHA, the regulated industry, the manufacturers of genomic technologies, and environmental and "watchdog" groups.

- **Fast track promising applications.**

We know from past experiences with environmental technologies that the path to commercialization is tenuous, long, and often riddled with regulatory uncertainty. New approaches end up competing with older ones that have been effectively "locked in" through regulation and organizational culture. The government needs to begin now to identify promising applications, possible early adopters, and potentially large markets that might be of interest to commercial firms.

The new EPA Interim Genomics Policy (*see related story p*) states that "EPA will consider genomics data on a case-by-case basis." How many "cases" are likely to appear on EPA's front door? FDA experiences have shown that drug companies have been reluctant to come forth to share genetic data with FDA regulators and we may expect similar hesitation on the part of the regulated industry. EPA should consider the creation of "safe havens" to encourage initial explorations of the use of genetic information in regulatory settings, an idea that has been floated at FDA.

Initially, it may make more sense to focus on non-regulatory applications for these technologies or piggyback off of other initiatives such as bioterrorism where both funding and perceived demand can be leveraged. Recently Lawrence Livermore Labs developed a multipathogen screening array using a commercially available Affymetrix Genechip© that can rapidly speciate a dozen biological pathogens in air, water, or soil. Could a similar device be designed to help screen key pathogens in the thousands of small community water supplies across the U.S.?

- **Establish an <u>on-going</u> function to examine ethical, social, and legal issues arising around toxicogenomic applications.**

The increasing use of genomic data for environmental purposes will raise a host of social and ethical issues. The boundaries between diagnosis and screening or between therapy and enhancement will be thin and fluid. The potential for genetic discrimination will pose a real danger. Society needs an on-going mechanism to address these issues. To be effective, such a function would have to involve multiple agencies (EPA, NIEHS, FDA, OSHA, and DOE) as well as academics, industry representatives, and members of the NGO and environmental justice communities. This poses a difficult organizational design challenge. It is doubtful that such a group organized under FACA provisions by a single agency could address the breadth of issues likely to arise or serve the broad interests of the many communities potentially impacted. Other options need to be explored, including the formation of a standing, but informal group, receiving support from multiple agencies and/or foundations.

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- **Do not forget ecology.**

Ecologists are familiar with their sideline position in risk assessment debates and toxicogenomics is no exception. However, it is possible that the greatest near-term utility of genomic technologies may be in improving our assessment of ecosystem impacts. We need to strategically identify and sequence the genomes of key indicator or sentinel species that could be used to more systematically assess ecosystem health. Non-regulatory, ecological applications of genomics need to be serious explored and funded, an area where leadership by EPA is needed and, again, coordination with other agencies like NIEHS, NSF, and DOE (Microbial Genome Project).

- **Educate policymakers and other relevant stakeholders.**

Environmentally relevant information may increasingly appear in clinical settings. Most doctors, nurses, and paramedical personnel receive no training on environmental issues yet they may, in the future, be on the front line in terms of delivering information to patients. Lay people, in general, will need better information to make informed decisions about exposures and strategies to reduce risks. The probabilistic nature of much of this data will be a real and continuing challenge to communication and understanding.

It is highly likely that genomics data will be used in toxic tort litigation in the future. The 1993 Supreme Court decision in *Daubert v. Merrell Bow Pharmaceuticals* has placed judges in a more prominent role as "gatekeepers" of scientific evidence in the courts. As complex genetic information finds its way into tort cases, judges will have to be better informed to decide on the admissibility of such evidence.

Few public policy makers have backgrounds in biology, let alone human genetics. The learning curve in genomics is steep and littered with an arcane vocabulary and complex concepts. Educational strategies for congressional members and policymakers in the executive branch are needed. Finally, an effort should be made now to begin educating the next generation of environmental professionals by developing course materials for environmental law and policy programs at leading universities.

- **Expand the boundaries of the debate on genomics and the environment.**

There are a number of areas that need to be put squarely on the table during future meetings. First, the discussions have focused almost exclusively on genomics and risk assessment, not intervention. Yet the science will lead us down a path where molecular and genetic intervention will be possible in the future, to block exposures inside the human body, repair environmentally-damaged DNA, etc. As we move from screening to prevention to therapy, the likelihood of evermore serious ethical implications will increase. Secondly, the discussions have been U.S.-centric. The global debate around genetically modified organisms (GMO's) should have taught us a lesson: that significant cultural differences exist even among developed nations concerning the application of

genetic science and technologies. These need to be taken into account as well as the implications of these approaches for the developing world. Finally, we are too willing to assume benign intent. We need to seriously consider how the science could be misinterpreted and misused, i.e., "junk" science, or abused for malicious intent, i.e. bio/ecoterrorism.

The science of genetics is complex, the technological advance rapid, and the potential social impacts great. How we confront the uncertainties and apply this new knowledge to environmental protection will provide a litmus test of the ability of our government to shape science for the public good in an era of radical transformations. For government to succeed in this task however, we will have to look far into the future, with many people, and with an open mind.